

Catalytic asymmetric synthesis of cyclopropane-carboxylic acids: an application of chiral copper carbenoid reaction

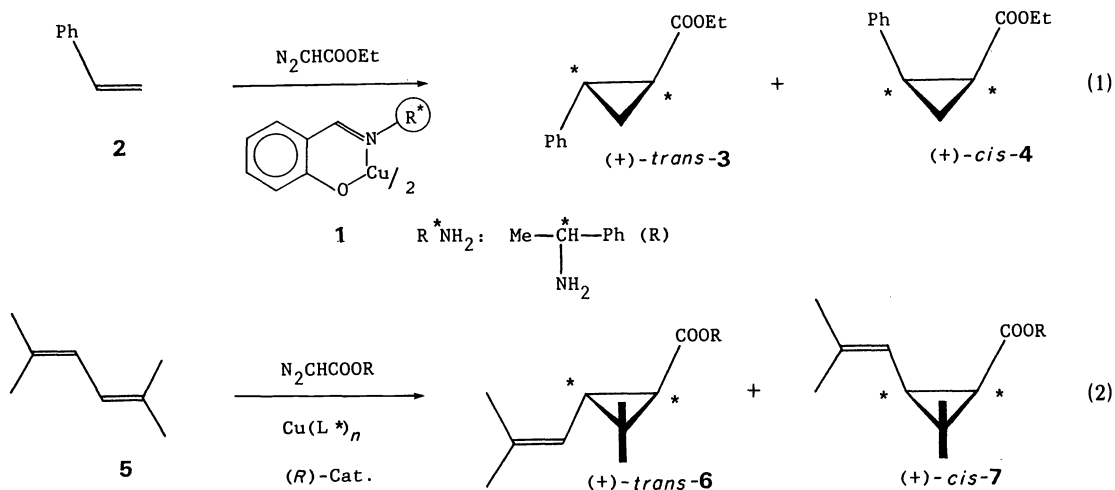
Tadatoshi Aratani

Takatsuki Research Laboratory, Sumitomo Chemical Co., Ltd.
 Takatsuki, Osaka 569, Japan

Abstract - Reaction of alkyl diazoacetate with an olefin catalyzed by a chiral copper complex gives an optically active alkyl cyclopropanecarboxylate. This chiral copper carbenoid reaction was successfully applied to the synthesis of industrially valuable cyclopropanecarboxylic acids: (+)-trans-chrysanthemic acid, (+)-cis-permethrinic acid and (+)-2,2-dimethylcyclopropanecarboxylic acid. A series of effective catalysts, chiral Schiff base-copper complexes, was prepared starting with an optically active α -amino acid to achieve more than 90% e.e. of the products. The chirality of the products was correlated with that of the catalyst on the basis of metallacyclobutane intermediates.

CHIRAL COPPER CARBENOID REACTION (ref. 1) AND ITS APPLICATION TO CHRYSANTHEMIC ACID SYNTHESIS

In 1966, the first example of asymmetric catalysis (ref. 2) by means of a soluble transition metal complex was reported by Prof. Nozaki and his coworkers. They decomposed ethyl diazoacetate in styrene in the presence of chiral copper complex (1) as a catalyst to give the products, trans- and cis-2-phenyl-cyclopropanecarboxylate (3 and 4), both in an optically active form (Eq 1). This finding demonstrated that the carbene derived from ethyl diazoacetate is not free but is combined with the chiral copper complex to form a carbene-copper complex (ref. 3), which is responsible for the asymmetric induction. Furthermore, the reaction provided a new method for the preparation of optically active cyclopropane derivatives of practical value, although the enantiomeric excess (e.e.) attained at that time was less than 10%.



Chrysanthemic acid, 2,2-dimethyl-3-(2-methylpropenyl)-cyclopropanecarboxylic acid (6, 7: R = H) is an acid component of pyrethroid, an insecticide of high activity and low mammalian toxicity (ref. 4). There is a close correlation between the chirality of a molecule and its biological activities. Among the four optical isomers of chrysanthemic acid, the most effective isomer is shown to be (+)-trans isomer, which is followed by (+)-cis isomer. (-)-Trans and (-)-cis isomers are almost ineffective (ref. 5). The natural chrysanthemic acid also has the (+)1R-trans configuration.

As an application of the chiral copper carbenoid reaction, alkyl diazoacetate was reacted with 2,5-dimethyl-2,4-hexadiene (5) in the presence of chiral copper catalyst to give an optically active alkyl chrysanthemate (Eq 2). The first problem to be solved was a choice of a suitable catalyst to achieve high e.e. of the product.

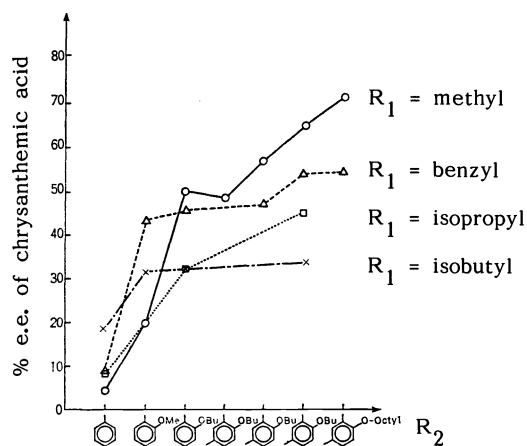


Fig. 2. Search for the catalyst.

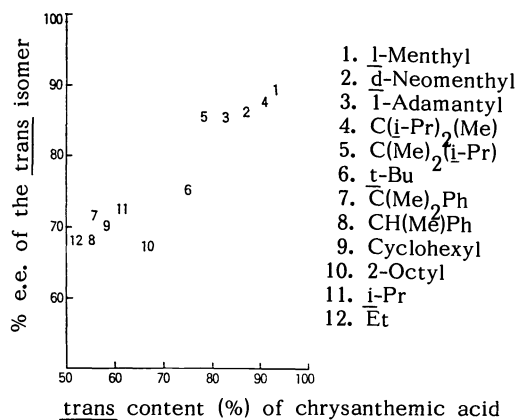


Fig. 3. Search for alkyl diazoacetate.

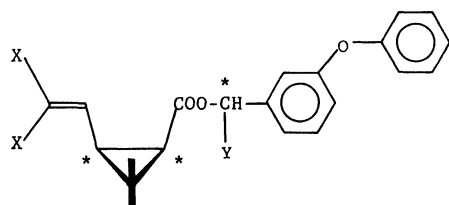
TABLE 1. Asymmetric synthesis of alkyl chrysanthemate

Alkyl	% Composition of chrysanthemic acid				cis/trans	% e.e.	
	(-)-cis	(+)-cis	(-)-trans	(+)-trans		cis	trans
Ethyl	9.2	39.4	8.1	43.3	49/51	62	68
<i>l</i> -Menthyl	2.0	5.4	2.7	89.9	7/93	46	94
<i>d</i> -Menthyl	5.8	22.6	3.4	68.2	28/72	59	90
<i>dl</i> -Menthyl	2.3	16.3	4.1	77.3	19/81	75	90

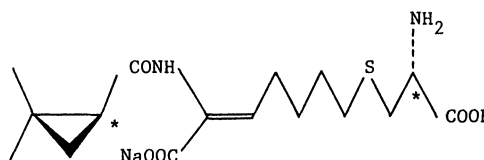
ASYMMETRIC SYNTHESIS OF CYCLOPROPANE CARBOXYLIC ACIDS

(ref. 11)

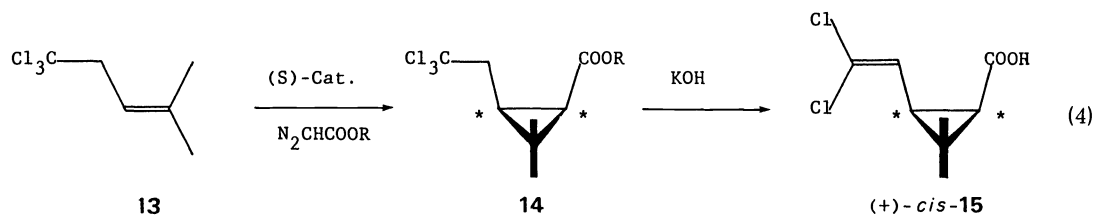
Permethrinic acid, 3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropanecarboxylic acid (15), is another kind of acid component producing pyrethroids (11) of higher potency and photostability (ref. 12). The most effective isomer of permethrinic acid is shown to be (+)1*R*-*cis* isomer. A stereoselective route to this isomer was explored using chiral catalysts at hand.



11, Permethrin (X = Cl, Y = H)



12, Cilastatin (MK-0791)

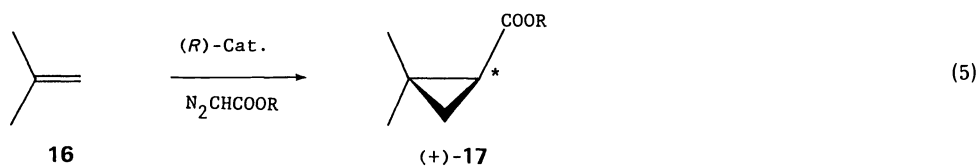


13

14

(+)-*cis*-15

(4)



16

(+)-17

(5)

Ethyl diazoacetate was reacted with 2-methyl-5,5,5-trichloro-2-pentene (13; ref. 13) in the presence of the catalyst of S configuration, S-1648, to give ethyl 2,2-dimethyl-3-(2,2,2-trichloroethyl)-cyclopropanecarboxylate (14), whose dehydrochlorination and hydrolysis with potassium hydroxide afforded (+)-permethrinic acid (Eq 4). Analysis of the product revealed that cis/trans ratio was 85/15 and e.e. of the cis isomer was 91%. This stereoselectivity makes a sharp contrast to that of chrysanthemate synthesis (Eq 2). First, thermodynamically less stable isomer, cis, is preferred in Eq 4 whereas thermodynamically more stable isomer, trans, is preferred in Eq 2. Second, preference of the same 1R configuration in the product requires S-catalyst in Eq 4 and the antipodal R-catalyst in the chrysanthemate synthesis. Since similar selectivity of Eq 4 was observed in the reaction of 2-methyl-2-butene (21; Table 2), these discrepancies cannot be attributed to the participation of chlorine atom of 13. An explanation will be given in the final section.

The third compound of practical importance comes from pharmaceutical field. Imipenem (MK-0787), N-formimidoyl-thienamycin, is one of the most promising β -lactam antibiotics recently developed (ref. 14). In spite of its high and wide antibacterial activity and strong resistance to β -lactamase degradation, Imipenem was susceptible to renal metabolism in animal species and in man. This metabolism can be suppressed by coadministration with Cilastatin (12), an enzyme inhibitor for dehydropeptidase I (ref. 15). (+)1S-2,2-Dimethyl-cyclopropanecarboxylic acid (DCCA, 17: R = H) is a key intermediate in the production of Cilastatin.

Ethyl diazoacetate was reacted with isobutylene in the presence of the catalyst, R-7644 (Fig. 1), to give ethyl ester of (+)-DCCA in 92% e.e. (Eq 5). This reaction was proved to work well in a factory scale. Other examples of asymmetric catalysis of practical usage include L-DOPA synthesis by Monsanto (ref. 16) and L-menthol production by Takasago (ref. 17).

The chiral catalyst 10 is useful in the preparation of optically active cyclopropanecarboxylic acids of a wide range (ref. 18). For example, L-menthyl diazoacetate was reacted with olefins in the presence of R- and S-1648 to give the corresponding cyclopropanecarboxylates in high e.e. The e.e. of the products was directly analyzed by GC and the absolute configuration was determined according to the literature. Results are summarized in Table 2.

TABLE 2. Asymmetric synthesis of substituted cyclopropanecarboxylic acids

Olefin	Catalyst Confign	Product <u>cis/trans</u>	(% e.e.)		Confign	
			<u>cis</u>	<u>trans</u>	<u>cis</u>	<u>trans</u>
Styrene (2)	R	14/86	(+)54	(+69	1S,2R	1S,2S
	S	18/82	(-)78	(-)81	1R,2S	1R,2R
1-Octene (18)	R	17/83	(+)46	(+76	1S,2R	1S,2S
	S	22/78	(-)64	(-)84	1R,2S	1R,2R
<u>trans</u> -4-Octene (19)	R	-	-	(+82	-	2S,3S
	S	-	-	(-)84	-	2R,3R
<u>trans</u> -Anethole	R	9/91	(+)44	(+81	-	-
	S	12/88	(-)60	(-)89	-	-
1,1-Diphenylethylene (20)	R	-	-	(+75	-	1S
	S	-	-	(-)64	-	1R
α -Methylstyrene	R	40/60	86	68	-	-
	S	36/64	68	58	-	-
2-Methyl-2-butene (21)	R	79/21	(+)ND	(+)ND	1S,3R	1S,3S
	S	77/23	(-)ND	(-)ND	1R,3S	1R,3R

STEREOCHEMISTRY OF CHIRAL COPPER CARBENOID REACTION

In this section, an attempt will be made to correlate the chirality of the products with that of the catalyst to deduce an empirical rule which predicts the absolute configuration of a new product (ref. 19). A mechanism is proposed to explain the mode of chirality transfer. Reactions employing the catalyst 10 of S configuration are considered throughout the following discussions. Enantio-preferences observed in Eqs 2, 4 and 5 and Table 2 are interpreted as follows. If prochiral olefins are placed on the plane as shown in Fig. 4, the carbene derived from alkyl diazoacetate prefers to cyclopropanate the olefins from the front side of the plane with the alkoxy-carbonyl substituent downward. When geometrical isomers of the product exist, the arrangement of the top gives the trans product and that of the bottom gives the cis product. Since the arrangements of top and bottom are upside down each other, both cis and trans products have the same absolute configuration at the carbene carbon atom. Thus, the olefin 5 gives 1S-trans- and 1S-cis-chrysanthemate (Eq 2; S Cat.) and the olefin 13 gives 1R-trans- and 1R-cis-15 (permethrinic acid precursor; Eq 4). What is the common feature of the arrangements of Fig. 4? This problem can be solved in terms of electronic factor of the olefin rather than steric one. Of the two olefinic carbon atoms, the carbon atom, α , capable to produce more stabilized carbonium ion is placed on the right side and the other, β , is placed on the left side (ref. 20). The order of stability of carbo-cation has been established as follows: benzylic \sim allylic > tertiary > secondary > primary. The conclusion is shown in Eq 6.

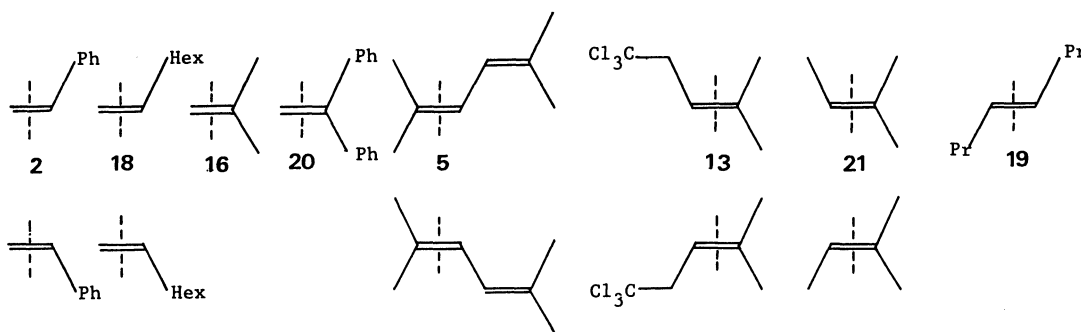
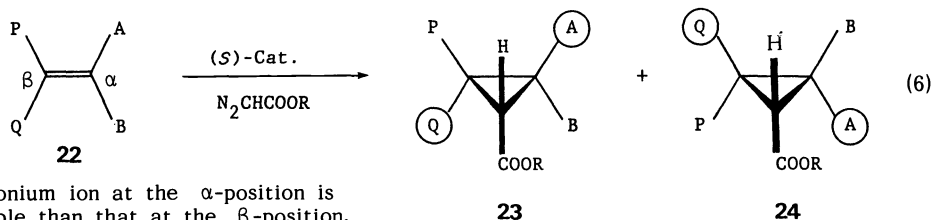
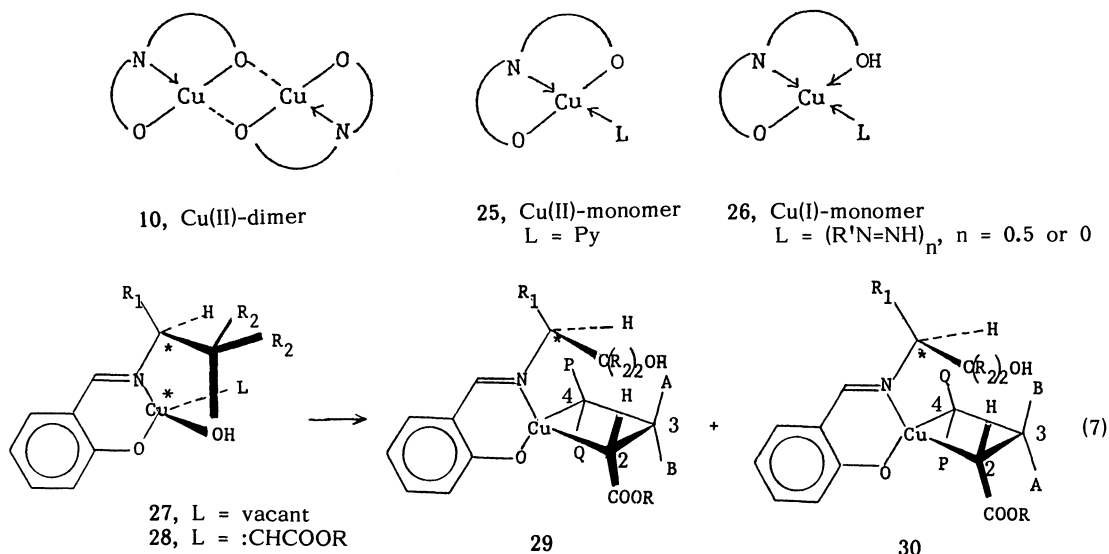


Fig. 4. The preferred arrangement of olefins for cyclopropanation



The carbonium ion at the α -position is more stable than that at the β -position.

There are strong evidences indicating that the original structure of copper complex 10 is not retained during the catalysis. First, the complex 10 should be activated before use. Thus, addition of alkyl diazoacetate to a solution of 10 at room temperature did not induce any changes. When the mixture was warmed up to 70–80 °C, a vigorous evolution of nitrogen gas took place and the color of the solution turned from green to brown. Subsequent addition of diazoacetate to the solution gave a smooth evolution of nitrogen gas. Second, a mononuclear complex (25), which was derived from the binuclear complex 10 upon the addition of a monodentate neutral ligand such as pyridine, gave the same result as 10 in the asymmetric synthesis. Finally, we found that reduction of cupric complex 10 with a substituted hydrazine gave a pale yellow cuprous complex (26; ref. 21), which induced an instantaneous decomposition of diazoacetate at room temperature. In conclusion, we are safe to assume that the actual catalyst responsible for the asymmetric induction is a mononuclear cuprous complex such as 27, in which copper is supposed to have a tetrahedral configuration and one of four coordination sites is left vacant.



Alkyl diazoacetate will attack the vacant site of 27 from the less hindered side (back side of the plane) to give a carbene-copper complex 28 with the evolution of nitrogen gas. Subsequent attack of an olefin occurs again from the back side of the plane (re-face) to give metallacyclobutanes (29 and 30; ref. 22), in which alkoxy carbonyl group comes to the bottom side of the metallacycle to avoid repulsion with the bulky $\text{C}(\text{R}_2)_2\text{OH}$ group. Nucleophilic nature of the attack of olefin controls regioselectivity in the metallacycle formation. Copper atom forms a bond with β -carbon atom of the olefin 22 rather than α -carbon atom. Collapse of the metallacycles 29 and 30 into the products 23 and 24, respectively, regenerates the true catalyst 27 to complete a catalysis cycle.

Geometry of the four-membered intermediate (29/30) is transferred into that of the three-membered products (23/24). Here is the reason why thermodynamically less stable *cis* product is favored in our permethrinic acid synthesis (Eq 4). The 2,4-*cis*-disubstituted metallacyclobutane 30 (A = B = methyl, P = trichloroethyl and Q = hydrogen), which is derived from the olefin 13, should be more stable than the 2,4-*trans* isomer 29. In Ciba-Geigy's *cis*-permethrinic acid synthesis (ref. 23), stability of the four-membered intermediate, *cis*-2-chloro-3,3-dimethyl-4-trichloroethyl-cyclobutanone is ascribed to a puckered conformation of cyclobutanone ring to release repulsion of two substituents at the 2,4-*cis* positions.

It is hoped that future experiments will prove the validity of stereochemical prediction (Eq 6) and the correctness of mechanistic pathway speculated herein (ref. 24).

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